CYTEC 201-13131

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ORIGINAL

July 20, 2001

Administrator
US Environmental Protection Agency
P.O. Box 1473
Merrifield, VA 22116

Attention: Chemical Right-to-Know Program/ Mr. Richard Hefter:

Dear Mr. Hefter,

I am writing to summarize Cytec's opinion that no further toxicity testing is necessary for 2-amino-2,3-dimethylbutanenitrile (CAS# 13893-53-3) because of its unique nature and the availability of surrogate data.. As discussed in Section C of the Robust Summary, 2-amino-2,3-dimethylbutanenitrile is an isolated intermediate manufactured under an extensive USEPA 5(e) Consent Order/SNUR and shipped under highly controlled transport provisions. Under the conditions of the Consent Order, stringent controls and conditions are prescribed for its manufacture, processing, distribution, use and disposal. As a result, the potential for exposure to humans or to the environment is minimal.

2-amino-2,3-dimethylbutanenitrile has unique hazard properties that warrant the many safeguards in place designed to prevent exposure to humans and the environment. However, we recognize that information is needed to evaluate hazards. As such, information has been developed to assess the potential hazards associated with the handling of this material during manufacture and in case of an accidental release. However, because of the acutely toxic properties of this material [the oral(rat) LD50 = 83 mg/kg[1], the dermal(rabbit) LD50 =23 mg/kg[2] (with death occurring within 24 hours of dose application), and a 4-hr inhalation (rat) LC50 = 73 ppm[3]] and the availability of surrogate teratogenicity data on nitriles we believe that a teratogenicity study and a chromosome aberration study will not contribute to a greater understanding of the hazards to human health or the environment associated with this material.

The purpose of **OECD Guideline 414**, Teratogenicity, is to assess the potential hazard to the unborn which may arise from exposure of the mother during pregnancy. Due to its high degree of acute toxicity and to the unlikelihood of this exposure scenario, we believe that an animal study of this nature would not change the already strict safeguards in place for the safe manufacture, handling, and transport of this material. In addition, the developmental toxicity potential of several aliphatic nitriles has been investigated in both *in vitro* and *in vivo* studies (Saillenfait 2000[4], Saillenfait 1993[5], Willhite 1981[6]).

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Although route and duration of exposure can affect the degree of toxicity, each nitrile investigated was demonstrated to produce adverse effects in the offspring. While mechanistic studies were not performed, metabolic release of cyanide has been implicated as a possible mechanism of the developmental toxic effects produced by some nitriles after maternal acute exposure. In studies with acrylonitrile or propionitrile, maternal administration of thiosulfate, a cyanide antagonist, provided partial protection against the teratogenic effects of these materials (Willhite 1981). This suggests that maternal production of cyanide may contribute to the developmental toxicity of nitriles.

2-amino-2,3-dimethylbutanenitrile is an aliphatic nitrile. In a hierarchy of aliphatic nitriles, aminonitrile would fall into the sub-family of saturated nitriles. Based on the data available, it can reasonably be assumed that all nitriles have the potential to produce similar adverse effects of embryolethality, fetotoxicity and teratogenicity in laboratory animals. This is reflected on the Material Safety Data Sheet for this product. Based on this surrogate data, additional research in this area is not warranted.

In light of this surrogate information the Developmental Toxicity section of the Data Summary and Test Plan for 2-amino-2,3-dimethylbutanenitrile has been amended. Please find both an electronic and paper copy of this revised document enclosed.

The purpose of **OECD Guideline 474** or **475**, Chromosome Aberration, is to screen for possible mammalian mutagens and carcinogens. We believe it is not necessary to conduct an experiment of this type because we already have evidence of no mutagenic activity from a Salmonella Reverse Mutation Assay. Due to the unique acute hazards associated with this material, long term exposure that could be associated with the development of chronic disease would not be encountered. Furthermore, results from this type of assay would not change the already strict safeguards in place for the safe manufacture, handling, and transport of this material.

In conclusion, we believe that further testing of this material to fulfill the two endpoints for which data has not been obtained is not warranted for the following reasons.

- Exposures resulting from chemical accidents are likely to be of relatively short versus chronic duration and 2-amino-2,3-dimethylbutanenitrile is estimated to have a half-life in the environment of ~44 hours. Thus, following an accident chronic exposures are not likely to occur due to its rapid degradation to HCN, ammonia, and methyl isopropyl ketone.
- Chemicals that liberate cyanide have demonstrated teratogenic potential in experimental animals. This is especially true of the aliphatic nitriles. Therefore we would not expect results to be different for aminonitrile.
- 2-amino-2,3-dimethylbutanenitrile is a liquid of low vapor pressure at ambient temperatures, rendering the risk of vapor inhalation relatively small. Some concentration of HCN (hydrogen cyanide) can exist above the liquid. HCN is a quick acting poison in that it is rapidly absorbed through unbroken skin and especially through the eyes.

- Chronic exposures are not likely in the workplace due to the stringent safety measures employed during manufacture and required by EPA regulation.
- This material is manufactured and transported under strict EPA mandated safeguards to eliminate any potential for human or environmental exposure.
- Conditions in which humans or the environment could be potentially exposed to 2-amino-2,3-dimethylbutanenitrile are limited and not likely to occur.

Therefore, in light of the nature of this material and the robust data already provided for the other 15 HPV endpoints required, we request that the tests for developmental toxicity and chromosomal aberration be waived.

I would be happy to discuss with you the results already developed and presented in our test plan should you have any questions. I can be reached directly at 973/357-3371.

Regards,

Lisa Navarro, Ph.D.
Manager, Toxicology Programs
Toxicology & Product Regulatory Compliance

[1] Acute Oral Toxicity of CL 94,149. American Cyanamid Company, March 4, 1983.

[2] Acute Dermal Toxicity of CL 94,149. American Cyanamid Company, March 4, 1983.

[3] Bushy Run Research Center Report # 51-611 for American Cyanamid Company, 1988.

[4] Saillenfait AM and JP Sabate (2000). Comparative developmental toxicities of aliphatic nitriles: in vivo and in vitro observations. *Toxicol Appl Pharmacol.* Mar 1, 163(2):149-163.

[5] Saillenfait AM, Bonnet P, Guenier JP, and J de Ceaurriz (1993). Relative developmental toxicities of inhaled aliphatic mononitriles in rats. *Fundam Appl Toxicol.* Apr, 20(3):356-375.

[6] Willhite CC, Fern VH, and RP Smith (1981). Teratogenic effects of aliphatic nitriles. *Teratology.* June, 23(3):317-323.